REMARKS/ARGUMENTS

Applicants thank the Examiner and her supervisor for conducting an interview with their attorneys on February 8. At the interview, references by Guerney, US 6,420,534, Powell, US6,319,689, and Chrysler, US 5,744,346 were discussed. Regarding Guerney, applicants noted that because all of the present claims are entitled at least to a priority date of June 15 via provisional application 60/139,172 (see the claim support summary table in the Appendix), Guerney was only citable under 35 USC 102(e) insofar as the disclosure of the '534 patent was reproduced in the priority application (USSN 60/101,594 filed September 24, 1998). It was pointed out that the priority document of Guerney (USSN 60/101,594 filed September 24, 1998) differed in many respects from the granted patent. Particularly, the priority document misidentifies the location of the transmembrane region of its isolated aspartyl protease (see p. 20), does not identify the signal sequence or pro region occupying amino acids 1-21 and 22-45 of the protein, misidentifies the function of its aspartyl protease as gamma secretase (see title), and does not express its aspartyl protease as a protein. It was further pointed out that in an office action in Guerney application 09/548,368, Examiner Turner rejected Guerney's arguments (presented by declaration) that he was entitled to priority for the "location of the transmembrane domain, or particular mutant lacking specific residues corresponding to the transmembrane domain and for deletion mutant lacking such specific residues which retain activity." Copies of the Guerney priority document, the declaration presenting Guerny's argument and the office action holding Guerney was not entitled to priority, as noted above, are cited on the attached supplemental IDS to complete the record.

It was also explained at the interview that Guerney's error in the identification of the transmembrane domain was not obvious to correct, because beta secretase is atypical of aspartyl proteases in having a transmembrane domain. It was further pointed out at the interview that Powell discusses a sequence of an aspartyl protease that differs from present SEQ ID NO:2 at codon 130. It was also pointed out that Powell does not identify his aspartyl protease as being beta secretase, or identify the transmembrane, signal or pro regions within it. It was further pointed out that the purity of beta secretase obtained by Chrysler was about 200-fold less than

the present case. It was also pointed out that the purification to homogeneity disclosed in the present case was achieved using affinity chromatography with a specific inhibitor (see Example 7 at p. 75) not discussed by Chrysler. Finally, there was some discussion of the issues of screening using transgenic mice. The Examiner suggested that more detail was needed regarding the description of such mice and the particulars of routes of administration and the like used in screening.

As discussed at the interview, independent claim 78 has been amended to specify that the protein comprises a segment of beta secretase extending from residue 46 to residue 452 or up to several amino acids beyond residue 452 of SEQ ID NO:2, but the protein lacks a transmembrane region. Support is provided by e.g., p. 31, lines 24-26 and p. 32, lines 2-5 explaining that segments of beta secretase terminating at residue 452 or even several amino acids beyond are particularly useful for crystallization studies because of the lack of a transmembrane domain that would interfere with crystallization. The claim has also been amended to recite lack of amino acids 1-45 rather than lack of amino acids 1-21 and 22-25 for simplicity and clarity. Claims directed to in vivo screening have been cancelled without prejudice as discussed below. Withdrawn claims have been cancelled except for claim 132, which it is submitted can be restored if the Examiner finds the generic claim allowable.

Applicants now turn to the specific issues raised in the office action.

1. 112, second paragraph

Claims have been amended as suggested.

1. Objections

The Examiner requests applicants to amend the description of Fig. 5 by replacing "contains" in the 8th line with "encodes." This objection is not understood because the description of Fig. 5 contains only 7 lines and does not use the word "contains." Clarification is respectfully requested.

2. Section 112, first paragraph

Claims 78, 81, 83-85 and 135 stand rejected for alleged lack of written description. The Examiner alleges that applicants have described insufficient species of beta secretase to support the claimed genus. The Examiner also alleges that either the beta secretase or substrate thereof must be defined in a novel and nonobvious manner.

In response the claims have been amended to specify a protein comprising a segment of a β-secretase enzyme protein extending from residue 46 to, or up to several amino acids beyond residue 452 of SEQ ID NO:2, but lacking a transmembrane region. Such a protein is novel and nonobvious for the reasons discussed above. Accordingly, it is not necessary to describe the substrate of beta secretase in greater detail.

Claim 81 stands rejected on the basis that applicants have not provided written description for the claimed genus of transgenic mice having APP transgenes. As discussed at the interview, several representative examples of such mice were known in the art, and cited in the specification providing support for the genus. Nevertheless, the claim has been cancelled to speed allowance of other subject matter.

Claim 135 stands rejected on the basis that applicants have not described a transgenic mouse containing any beta secretase. Claim 135 has been cancelled to speed prosecution.

Claims 78, 84 and 85 stand rejected because the specification does not provide enablement for any sequence of beta secretase. As noted, the claims have been amended to specify that a protein comprising a segment extending from residue 46 up to, or beyond residue 452 of SEQ ID NO:2, but lacking a transmembrane region. Such a protein has beta secretase activity (see sentence bridging pp. 31-32).

Claims 81, 83 and 135 stand rejected on the basis that the specification allegedly lacks enablement for in vivo screening. This rejection is in part based on alleged difficulties in producing transgenic mice, and also in difficulties in determining dosages, routes of administration and avoiding side effects. As was discussed at the interview, success of a

screening method does not require that one determine optimum dosages, routes of administration or freedom from side effects of each compound being screened. Rather, such a screen can be considered successful if it results in identification of but a single compound from a larger pool with a desired activity. Nevertheless, the above claims have been cancelled to speed prosecution.

Rejection under 35 USC 102

Claims 78 and 84 stand rejected as anticipated by WO96/40885. The '85 application is the corresponding PCT to Chrysler US 5,744,346 discussed at the interview. As was discussed at the interview, the present claims are distinguished over the '85 application because the claims specify lack of a transmembrane domain. Although the '85 application generically discusses beta secretase, it does not disclose a species lacking the transmembrane domain.

Rejection under 35 USC 103

Claim 85 stands rejected as obvious over the '85 application (applied as above) in further view of WO 98/37226. The '26 application is alleged to disclose substrates of beta secretase.

Claim 85 is nonobvious because the '85 application does not disclose a beta secretase enzyme lacking a transmembrane domain, and the secondary reference does nothing to compensate for this deficiency.

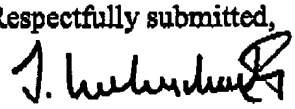
Moreover, applicants reiterate that identification of a transmembrane region its removal were not obvious because beta-secretase is atypical of other aspartyl proteases in having a transmembrane region, because Powell did not identify a transmembrane region at all, and Guerney misidentified the location of a transmembrane region. Also, the segment of beta secretase misidentified as a transmembrane domain by Guerney (residues 392-417 of SEQ ID NO:6) has 19/26 hydrophobic residues (*i.e.*., assuming the ordinary definition of hydrophobic amino acids: Pro, Phe, Trp, Met, Ala, Gly, Tyr, Ile, Leu and Val), so the characterization of this domain as a transmembrane domain is not obviously in error.

Obviousness-Type Double Patenting

Claim 78 stands rejected for obviousness-type double patenting over claim 1 of US 6,329,163. Claim 81 is rejected as obvious over claim 11 of the '163 patent. The claims of the '163 patent do not disclose or suggest that the claimed beta secretase lacks a transmembrane domain.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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